SOUTHWESTERN NEWS

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Overproducing leptin receptors in fat cells may be key to halting weight gain

DALLAS – Dec. 1, 2005 – A new study by researchers at UT Southwestern Medical Center suggests that when fat cells increase in size – as they do during the development of obesity – the cells progressively lose receptors for the hormone leptin, a powerful stimulus for fat burning.

Leptin, a hormone produced by the body's fat cells and involved in the regulation of body weight, was first discovered in 1994. It was thought leptin itself would be a key to curing obesity in humans, but the hypothesis did not readily translate into weight loss in obese people. Using mouse models, UT Southwestern researchers have now shown that if enough receptors are present on the fat cells, it is impossible for the cells to store fat and obesity would be blocked.

The new findings, appearing in an upcoming issue of the *Proceedings of the National Academy of Sciences* and currently available online, bring researchers a step closer to understanding obesity in humans, said Dr. Roger Unger, director of the Touchstone Diabetes Research Center at UT Southwestern and senior author of the study.

"We now think that people with naturally high levels of leptin receptors may not gain weight as rapidly over time as people who have low levels of leptin receptors," said Dr. Unger. "It could explain why some people can eat more and do not gain weight."

To test this hypothesis, the UT Southwestern researchers used genetically modified rats in which the leptin receptor remained present in large quantities even during marked overfeeding. In normal mice, the high-fat diet caused massive obesity with enlargement of fat cells to almost three times their normal size. In mice with the forced overexpression of the leptin receptor on their fat cells no obesity occurred, even though they too were fed high-fat, highly caloric diets.

"The fat-storing function of the fat cells requires the disappearance of the leptin receptor," Dr. Unger said. "This is done in order to block the action of the leptin fat cells produce."

May-Yun Wang, lead investigator and instructor of internal medicine at UT Southwestern, said the transgenic mice's high levels of leptin receptors caused all surplus calories to be burned rather than stored.

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"They were overfed tremendously and did not get obese. Our control animals were fed the same diet and gained an enormous amount of weight," Dr. Wang said. "If we could prevent the disappearance of leptin receptors in people who overeat, they would likely not gain weight after overeating."

In terms of evolution, researchers reasoned that the ability of leptin receptors to disappear during overeating provided fat cells with a vital mechanism to defend against famine by efficiently storing calories whenever nutrients were abundant.

On the other hand, overweight and obese humans, like rodents, have high levels of leptin and low numbers of receptors, Dr. Unger said. The inverse relationship between high leptin and its receptor may explain the failure of most obesity treatment with leptin. The common pattern is a modest weight loss followed by regaining the weight, which may be a function of declining leptin receptor levels.

Currently 50 million Americans suffer from metabolic syndrome – a disease associated with obesity and encompassing coronary artery disease and type 2 diabetes.

"If we had a pharmacologic way of manipulating the expression of the leptin receptor we might be able to control obesity," Dr. Unger said. "However, by far the best treatment for obesity will always be caloric restriction and regular exercise."

Researchers Lelio Orci and Mariella Ravazzola at the University of Geneva Medical School in Switzerland also contributed to the study.

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